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The Behavioral Characteristics of Sotos Syndrome

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ABSTRACT

In this study we describe the levels of clinically significant behavior in participants with Sotos syndrome relative to three matched contrast groups in which the behavioral phenotype is well documented (Autism Spectrum Disorder, ASD; Prader-Willi and Down Syndromes). Parents and carers of 38 individuals with Sotos syndrome (mean= 17.3; SD=9.36), completed questionnaires regarding self-injury, aggression, repetitive behavior, autism spectrum phenomenology, overactivity, impulsivity and mood, interest and pleasure. Individuals with Sotos syndrome showed an increased risk of self-injurious behavior, physical aggression and destruction of property relative to the Down syndrome group but not a greater risk of stereotyped behavior. Impulsivity and levels of activity were also significantly higher relative to those with Down syndrome and comparable to those with ASD. A large proportion of participants met the cut off score for ASD (70.3%) and Autism (32.4%) on the Social Communication Questionnaire. Social impairments were particularly prominent with repetitive behavior and communication impairments less characteristic of the syndrome. Interestingly, preference for routine and repetitive language were heightened in individuals with Sotos syndrome and the repetitive behavior profile was strikingly similar to that observed in individuals with Prader-Willi syndrome. These findings build upon previous research and provide further evidence of the behavioral phenotype associated with Sotos syndrome.

Key words: Sotos syndrome, behavioral phenotype, challenging behavior, repetitive behavior, autism spectrum disorder characteristics, NSD1 mutations.

INTRODUCTION

Sotos syndrome was first described in 1964 as an overgrowth disorder with variable level of intellectual disability. Kurotaki et al. (2002) reported both 5q35 deletions and mutations of the NSD1 gene as the primary cause of Sotos syndrome. The NSD1 genetic mutation has not been identified in all individuals with a clinical presentation and diagnosis of Sotos syndrome, although it is likely that these cases probably do have Sotos syndrome and will represent a phenocopy. In some research reports, NSD1 mutation negative cases are used as a comparison group for those who are NSD1 mutation positive.

The characteristics which typify Sotos syndrome include advanced skeletal maturation as a consequence of accelerated overgrowth particularly in early infancy (Wit et al., 1985); long narrow face, high forehead, frontal bossing, high arched palates, prominent jaws and an unusually large head (Cole & Hughes, 1991; 1994); large hands and feet from birth (Hook and Reynolds, 1967) and intellectual disability of varying degrees (Tatton-Brown et al., 2004). Delayed motor skill development has been reported across a majority of studies, with younger children displaying early psychomotor delay (e.g. Bloom, 1983; Leventopolous et al., 2009) and clumsiness reported in older children (e.g., Bale et al., 1985; Trad et al., 1991). Improvement has been observed during adolescence (Mauceri et al., 2000). Interest in describing the behavioral phenotype of Sotos syndrome has increased recently, particularly with regard to those with and without confirmed NSD1 mutations and deletions (de Boer et al., 2006).

The literature on the behavioral phenotype of Sotos syndrome is limited to a small number of studies investigating the cognitive and behavioral characteristics via case and cohort studies. Of the behaviors recorded, the most widely reported include communication impairments (e.g. Ball et al., 2005), atypical social behavior (e.g., Ratter & Cole, 1991; Sarimski, 2003), ADHD and hyperactivity (e.g., Finegan et al., 1994; Varley & Crnic, 1984) with over half of all studies reporting these behaviors.

Studies investigating communication and language skills in Sotos syndrome indicate characteristic difficulties in speech articulation including delayed or no speech development (Compton et al, 2004; Morrow et al., 1990; Okamoto, 2010) and limited expressive language (Bale et al., 1985; Mauceri et al., 2000; Mourisden & Hansen, 2002). The most extensive cohort study by Ball et al. (2005) reported that individuals with Sotos syndrome showed greater impairments in expressive and receptive language compared to the normative sample. In contrast, two cohort studies (Finegan et al., 1994; Sarimski, 2003) found there to be no deficits in language.

The investigation of atypical social behavior has used a variety of methods such as observation (e.g., Mourisden & Hansen, 2002), parental reports (e.g., Mauceri et al., 2000; Rutter & Cole, 1991) and standardized measures (e.g., de Boer et al., 2006; Finegan et al., 1994; Sarimksi, 2003). Two cohort studies (de Boer et al., 2006; Finegan et al., 1994) reported individuals with Sotos syndrome to score higher on the 'social scale' of the Child Behavior Checklist (CBCL, Achenbach, 1991a,b) compared to the CBCL's normative sample and a range of observational studies have described social difficulties including social withdrawal (e.g. Varley & Crnic, 1984; Mourisden & Hansen, 2002) and difficulties making close friends (e.g., Rutter & Cole, 1991; Sarimski, 2003; Compton et al., 2004).

Studies have generally reported higher levels of ADHD and/or hyperactivity in participants with NSD1 mutations (i.e. Sotos syndrome) when compared to non NSD1 mutation overgrowth cases (de Boer et al., 2006). Other difficulties reported in participants with NSD1 mutations (vs. NSD1 non-mutations) include aggressive behavior (e.g. de Boer et al., 2006; Mauceri et al., 2000; Finegan et al., 1994) with 55% of individuals with NSD1 mutations showing more aggression than typically developing controls as measured on the CBCL. Observations of temper tantrums (e.g. Compton et al., 2004; Rutter & Cole, 1991), repetitive behaviors (Finegan et al., 1994; Sarimski, 2003; Trad et al., 1991), psychosis (Kessler & Kraft, 2008) and Autism Spectrum Disorder characteristics (Leventopolus et al., 2009; Morrow et al., 1990; Zappella, 1990) are also described

Over half of the studies investigating behavior in Sotos syndrome have adopted a case study methodology. However, the limitations of this approach make it difficult to generalize the findings because small numbers of participants and assessments based on clinical judgment or observation make replication difficult. Although, the use of cohort methodology may address some of these difficulties, such as employing standardized measures and adopting larger participant numbers (e.g., Finegan et al., 1994; Sarimski, 2003), many of the behaviors are still not well defined (e.g., social impairment, aggression). In addition, some of the measures, even though standardized, may not be designed to be used for an intellectual disability population, hindering the ability to make credible comparisons and generalizations. Finally, only three studies of individuals with Sotos syndrome have employed matched comparison groups (e.g., de Boer et al., 2006; Finegan et al., 1994; Sarimski, 2003). The use of comparison groups is now common in behavioral phenotype research designs. The conceptualization of behavioral phenotypes typically incorporates the notion of difference between people with a given syndrome, and those without the syndrome, who are comparable with regard to characteristics associated with difference within the population of people with comparable level of intellectual disability (Dykens, 1995). Comparison groups are usually matched for mental and chronological age and composed of participants with heterogeneous etiology. However, an alternative approach, which is broadly consistent with the perspective adopted by Dykens, is the use of contrast groups of different genetic disorders (Oliver et al., 2011). For the purpose of the present study, individuals with Down and Prader-Willi syndromes and Autism Spectrum Disorder (ASD) were used as contrast groups because they experience the same range of level of ability as individuals with Sotos syndrome and the behavioral phenotype of each disorder has been well documented. This methodology allows the positioning of Sotos syndrome relative to other genetic syndromes on given constructs.

Prader-Willi syndrome is associated with mild to moderate intellectual disability and the main cause is the physical or functional loss of genetic information on chromosome 15 in the q11–

q13 region (e.g. Whittington et al., 2004). The behavioral phenotype includes temper outbursts, repetitive questioning, excessive eating, specific repetitive and self-injurious behaviors, mood disturbance, 'stubbornness', 'disobedience', excessive daytime sleepiness and under activity (Oliver et al., 2013). ASD is a pervasive developmental disorder with a broad array of behavioral differences. These include; impairments of social interaction and communication and restricted, stereotypical, and ritualized patterns of behavior (Bailey et al., 1996). Intellectual disability is also associated with Autism Spectrum Disorder with approximately two-thirds of individuals having an intellectual disability (Smalley, 1997). Down syndrome is the most common genetic syndrome and is caused by an extra chromosome 21 (trisomy 21) in 95% of individuals (Fidler, 2005) and is associated with characteristic facies (e.g. short stature, flat facial profile, small ears, protruding tongue) and intellectual disability. Distinct behaviors reported in individuals with Down syndrome include; high sociability (e.g., Jahromi et al., 2008), high rates of self-talk (e.g., Glenn & Cunningham, 2000), noncompliance, attention problems, and compulsions (e.g., Coe et al., 1999; Evans & Gray, 2000). Various behaviors have also been noted to increase with age include anxiety, depression and withdrawal (Feeley & Jones, 2006).

The primary aim of this study was to describe the levels of clinically significant behavioral disorders in participants with Sotos syndrome. The secondary aim was to compare the behavioral characteristics of Sotos syndrome with that of individuals with ASD, Down and Prader-Willi syndromes, selected because they each have a well-established and defined behavioral phenotype.

METHODS

Ethical approval

Ethical review was provided by the Coventry Research Ethics Committee.

Recruitment

Participants with Sotos syndrome were recruited though three different sources: the Child Growth Foundation (CGF; an independent charity supporting children, families of children and adults with growth related problems), the Clinical Genetics Department at Birmingham Women's Hospital and the Clinical Genetics Department at Liverpool Alder Hey hospital. Although NSD1 gene status was not available, all participants had a confirmed diagnosis of Sotos syndrome by a clinical geneticist or pediatrician. In total, 152 questionnaire packs were sent out and 42 packs were returned (27.63% return rate). Data regarding the three contrast groups (Prader-Willi syndrome, ASD and Down syndrome) was taken from a substantive, pre-existing database of individuals who had taken part in previous research investigating behavioral phenotypes (e.g., Oliver et al., 2011; Burbidge et al., 2010; Arron et al., 2011; Moss et al., 2009).

Procedure

In order to protect confidentiality, questionnaire packs, which included a covering letter, consent forms, information sheets and a prepaid return envelope, were sent out to parents and carers of individuals with Sotos syndrome via each source of recruitment. Parents and carers were asked to complete and return the questionnaire pack along with the consent form. A follow up letter was sent out to participants one month after the questionnaire packs had been sent to improve the return rate.

Participants

+++insert table I about here+++

Participants in the Sotos syndrome group were matched individually to participants with Prader-Willi syndrome, Down syndrome and ASD on age, gender and level of ability (as based on the Wessex Scale; Kushlisk et al., 1973). Thirty-eight individuals with Sotos syndrome were matched to 38 individuals with Down syndrome, 38 individuals with Prader-Willi syndrome and 36 individuals with ASD.

The mean age of the 150 participants was 17.3 years (SD= 9.36 years), with 67% of the sample male. The Wessex Scale (Kushlick, Blunden & Cox, 1973) was used to describe speech, vision, hearing impairments and level of self-help skills. In total, 84% of all participants were reported to be able or partly able with regard to self-help skills, 97% were described as 'verbal', 90% of all participants were 'mobile', 71% had normal vision and 83% had normal hearing. Descriptive data including mean age and range, gender, level of self-help ability, mobility, vision, hearing and speech are shown in Table I.

Measures

Data from seven questionnaires are reported in the present study:

The Demographic Questionnaire

The demographic questionnaire reported basic details such as date of birth, gender, mobility, verbal ability (i.e. able to communicate more than 30 signs/words) and diagnostic status (whether given, by whom and when).

The Wessex Scale (Kushlick et al., 1973)

The Wessex scale is designed to be completed by parents and carers to assess the level of adaptive behavior in participants. This is achieved by evaluating the physical and social abilities of individuals on subscales including self help skills, continence, mobility, speech and literacy. The

measure has good inter-rater reliability with children and adults, at both the item and subscale level (Kushlick et al. 1973; Palmer & Jenkins 1982).

The Activity Questionnaire (TAQ; Burbidge & Oliver, 2008; Burbidge et al., 2010)

The Activity questionnaire is completed by parents and carers of individuals with intellectual disability and is suitable for use with both non-verbal and verbal individuals. The questionnaire evaluates hyperactivity and impulsivity on 18 items across three subscales: impulsivity, over-activity and impulsive speech. Robust internal consistency and reliability has also been established (Burbidge et al., 2010)

The Repetitive Behaviour Questionnaire (RBQ; Moss and Oliver, 2008; Moss et al., 2009)

The Repetitive Behaviour Questionnaire is an informant based questionnaire which identifies specific types of repetitive behavior in both children and adults with intellectual disabilities. The questionnaire is made up of nineteen operationally defined and observable behaviors across five subscales: restricted preferences, repetitive speech, insistence on sameness, stereotyped behavior and compulsive behavior. A five point Likert rating scale is used to record responses which range from ‘never’ to ‘more than once a day’. Other studies have also shown the questionnaire to have good reliability and validity (Moss et al., 2009).

The Challenging Behaviour Questionnaire (CBQ; Hyman et al., 2002)

The Challenging Behaviour Questionnaire is a brief measure designed to assess the presence or absence of different behaviors over the past month. Behaviors include physical and verbal aggression, self-injury and destruction of property. Good inter-rater reliability has been established (Hyman et al., 2002).

Mood, Interest and Pleasure Questionnaire Short Version (MIPQ-S; Ross & Oliver, 2003; Ross et al., 2008)

The Mood, Interest and Pleasure Questionnaire evaluates two constructs associated with depression in adults and children with intellectual disabilities. Informants are required to rate 12 items based on retrospective observations over a two week period. The questionnaire shows good internal consistency and reliability (Ross & Oliver, 2003).

Social Communication Questionnaire (SCQ; Rutter et al., 2003)

The Social Communication Questionnaire (SCQ) is a screening tool designed to measure communication and social skills in participants suspected of having ASD. The questionnaire is comprised of three subscales: communication, social interaction and repetitive and stereotyped behaviors. Higher scores signify the presence of abnormal behaviors, with scores of 15 and above discerning individuals with an ASD and 22 and above indicating Autism. The SCQ was shown to have good concurrent validity with the Autism Diagnostic Observation Schedule and Autism Diagnostic Interview (Berument et al., 1999; Howlin & Karpf, 2004).

Data Analysis

All data were tested for normality using Kolmogorov-Smirnov tests. Data which were not normally distributed ($p<.05$) were analyzed using non parametric tests. The percentage of individuals showing self-injurious behavior, physical aggression, stereotyped behavior and property destruction in each group was derived from the Challenging Behaviour Questionnaire. Chi-square tests were used to evaluate group differences in prevalence rates of these behaviors. Further evaluation using Odds ratio analysis in which the risk of challenging behavior in Sotos and Prader-Willi syndromes and individuals with ASD was calculated relative to the Down syndrome group was also conducted.

One Way ANOVAs and Sheffé post hoc tests were carried out at subscale level on the Social Communication Questionnaire, The Activity Questionnaire and Mood, Interest and Pleasure Questionnaire-Short form to identify areas of difference on affect, impulsivity, over-activity and autism spectrum characteristics across the groups. Analysis of the Social Communication Questionnaire was repeated including only those individuals who met the cut off score for ASD in each syndrome group, in order to evaluate the profile of autism spectrum symptomatology across the groups whilst accounting for the heterogeneity within each of the groups regarding severity of these characteristics. Scores on the Repetitive Behaviour Questionnaire were compared across groups using Kruskal-Wallis tests and pair-wise Mann-Whitney U post hoc comparisons on full scale, subscale and item levels.

A conservative alpha level of <.01 was employed for all primary analyses. Post-hoc contrasts were tested at $p<.05$ for all analyses with the exception of the Repetitive Behaviour Questionnaire item level analysis, which employed a <.01 *p* value for post hoc contrasts due to the number of items and comparisons.

The findings from the above analyses are reported below alongside figurative illustrations of the behavioral phenotype profiles for each of the four syndrome groups.

RESULTS

Demographic Characteristics

Demographic data for the four syndrome groups are presented in Table I. A one-way ANOVA revealed no significant group difference on chronological age. Chi-square tests demonstrated no significant group differences on gender, level of ability, vision and speech. Significant differences were observed for mobility and hearing. Post-hoc comparisons highlighted significantly higher levels of mobility in participants with Sotos syndrome, Down syndrome and the ASD group

compared to those with Prader-Willi syndrome. The Sotos and Down syndrome groups also had significantly poorer hearing than the ASD and Prader-Willi syndrome groups.

Prevalence of self-injurious, aggressive, destructive and stereotyped behavior

+++Insert table II about here+++

To examine self-injurious, aggressive, destructive and stereotyped behaviors across the groups, odds ratio's and 99% confidence intervals were used to calculate the likelihood of individuals displaying these behaviors associated with self-injury, aggression, destruction of property and stereotyped behaviors. These were compared to participants in the Down syndrome group (see Table II). As is evident in Table II, participants in the Sotos Syndrome group showed an increased risk of self-injurious behavior, physical aggression and destruction of property relative to the Down syndrome group but did not demonstrate a greater risk of stereotyped behavior. Stereotyped behavior was also significantly less frequent in Sotos syndrome compared to the ASD group. Prader-Willi syndrome showed the highest rate of self-injurious behavior.

+++Insert table III about here+++

Table III displays the mean subscale scores and results from group comparisons for the TAQ, MIPQ-S and SCQ.

Impulsivity and Overactivity

As seen in Table III, there were significant group differences on the impulsivity and overactivity subscales and the total activity score of the TAQ. No significant group differences were found on the impulsive speech subscale. Post hoc analyses indicated that participants with Sotos syndrome scored significantly lower on overactivity and total activity scores compared to participants with ASD but they scored significantly higher than participants with Down syndrome on impulsivity and the total activity score.

Mood, Interest and Pleasure

Significant group differences were found on the mood, interest and pleasure subscales and on the total MIPQ-S score. Post hoc analyses revealed the Sotos syndrome group to show significantly higher scores on this measure compared to the ASD group. This suggests that individuals with Sotos syndrome group experience greater pleasure and interest in activities and show a more general 'positive' mood than those with ASD.

Autism Spectrum Disorder and Autism

+++Insert Table IV about here+++

Table IV shows the proportion of individuals in each group who met the cut off for ASD and Autism on the Social Communication Questionnaire. A large proportion of participants with Sotos syndrome scored at the clinical cut off for ASD (70.3%) and Autism (32.4%).

Analysis of scores on the SCQ (see Table III) indicate significant group differences on the total SCQ score and all SCQ subscales (communication, restricted, repetitive & stereotyped behavior and reciprocal social interaction). Post-hoc analyses revealed that participants with Sotos syndrome scored significantly lower than participants with ASD and significantly higher than the DS group on the repetitive behavior subscale and the total SCQ scores. No significant differences between the Sotos syndrome and ASD groups were identified for the communication and social interaction subscales. The ASD group scored significantly higher than the Prader-Willi and Down syndrome groups on all subscales of the SCQ and the total score.

When participants who did not meet the cut off score for ASD were excluded from the analysis, there were no significant group differences on any of the subscale scores (Communication: $F_{(3,91)} = .67$; $p = .58$; Repetitive behavior: $F_{(3,91)} = 2.91$; $p = 04$; Social interaction: $F_{(3,91)} = 1.09$; $p = .36$) or on the total score of the SCQ ($F_{(3,91)} = 1.07$; $p = .37$). This suggests that individuals with Sotos, Prader-Will and Down syndromes who show clinically relevant levels of ASD characteristics (indicated by attaining the ASD cut off score on the SCQ) show a similar level of symptom severity in all domains of the triad of impairments compared to individuals with idiopathic ASD.

Repetitive Behaviors

+++Insert table V about here+++

Full-scale and Subscale Level Analysis

Scores on the RBQ were compared across groups. Full scale, subscale and item level scores were evaluated using one way analysis of variance and Scheffé post hocs (see Table V).

Significant differences were identified on all RBQ subscale and total scores, with the exception of the restricted preferences subscale. Individuals with Sotos syndrome scored significantly lower than the ASD group on stereotyped behavior. However, the Sotos syndrome group scored significantly higher than the Down syndrome group on repetitive use of language. The Down syndrome group scored significantly lower than the ASD group on all subscales and total scores.

Item Level Analysis

+++Insert Table VI about here+++

Item-level scores were compared for participants for each group using Kruskal-Wallis analysis and paired post-hoc comparisons (see Table VI). Significant group differences were revealed on 7 items (object stereotypy, body stereotypy, hand stereotypy, hoarding, preference for routine, repetitive questions and repetitive phrases/signing). The Sotos syndrome group scored significantly lower than the ASD group on object and body stereotypy and significantly higher than the Down syndrome group on items referring to preference for routine, repetitive questions and repetitive phrases/signing. The Sotos syndrome group scores were comparable to that of the ASD and Prader-Willi syndrome groups on these items. The Prader-Willi syndrome group showed significantly more hoarding behaviors than the ASD and Down syndrome groups.

Figure 1 depicts the repetitive behavior profile of each group, describing the profile for each group on the mean item level scores where the shaded areas represents the five different subscales of the Repetitive Behaviour Questionnaire. The figure demonstrates the heterogeneous profile patterns and greatest number of topographies of repetitive behavior for each of the 4 participant groups. The positive (‘+’) and negative (‘-’) symbols, next to certain item subscales on each behavioral profile, indicates their specificity relative to each syndrome

group. The figure highlights the similarities regarding repetitive questioning and preference routine in the Sotos syndrome and Prader-Willi syndrome.

+++Insert Figure 1 about here+++

DISCUSSION

This is the first study that describes the behavioral features of individuals with Sotos syndrome using standardized questionnaires appropriate for individuals with intellectual disabilities and contrasts individuals with Sotos syndrome to those with other genetic syndromes and ASD, for which behavioral phenotypes are well documented. Participants in this study were matched carefully on the basis of chronological age, gender, level of ability and speech. Matching by age, gender and ability allows for significant group differences on dependent variables to be more likely attributable to the presence of the syndrome rather than a broader intellectual disability or other confounding factor (Berney, 2003).The aims of this study were to describe the levels of clinically significant behavioral difficulties and disorders in participants with Sotos syndrome and compare the behavioral phenotype of participants with Sotos syndrome with three different groups of genetic syndromes for which the behavioral phenotype has already been well described.

In the current study, three forms of clinically significant behavior were shown to be more likely to occur in participants with Sotos syndrome than those with Down syndrome including self-injurious behavior, stereotyped behavior and destruction of property. These behaviors were found to occur in almost 42-43% of participants with Sotos syndrome. The findings are consistent with previous reports of aggression and extend previous descriptions of challenging behavior by reporting high levels of self-injury in this population. The prevalence of self-injury in participants with Sotos syndrome was found to be broadly comparable to that of participants in the ASD and Prader-Willi syndrome contrast groups, although stereotyped behavior was less frequent. This suggests these behaviors are relatively prevalent in Sotos syndrome. Given that reports of self-injurious behavior have not previously been noted within the literature, this is surprising. Research aimed at gaining a greater understanding of what might underpin self-injurious behavior in this group should be a priority.

This study provides evidence for high levels of impulsivity and overactivity seen in participants with Sotos syndrome, with scores comparable to those of individuals with ASD in which high levels of these behavioral difficulties are well established (Aman, 2004; Bradley & Isaacs, 2006). These findings are consistent with previous descriptions of individuals with Sotos syndrome (e.g., deBoer et al., 2006; Finegan et al., 1994; Rutter & Cole, 1991; Varley & Crnic, 1984). However, this is the first study to identify a heightened prevalence of impulsivity and activity in Sotos syndrome relative to other syndrome group populations. Nonetheless, this area is still poorly described in the literature, and would benefit from future research.

A large proportion of participants with Sotos syndrome met the cut off level for ASD (70.3%) and Autism (32.4%) on the Social Communication Questionnaire. These levels were substantially higher than those reported for Down and Prader-Willi syndromes. The proportions meeting cut off in Down syndrome were similar to those reported by others (e.g. DiGuiseppi et al., 2010; Lowenthal, et al., 2007; Moss et al., 2013; Starr et al., 2005), hence the base levels across the syndrome groups, including Sotos syndrome, would appear to be useful comparative estimates. Domain level analyses revealed significantly higher scores in the Sotos syndrome group relative to the Down syndrome group in the social interaction domain of the Social Communication Questionnaire, with scores comparable to the ASD group on this domain. Interestingly, the Sotos syndrome group scored significantly lower than the ASD group on the repetitive behavior domain, suggesting that impairments in social interaction may be more prominent relative to other areas of the triad of impairments. Previous research has reported social impairments in Sotos participants, although the supporting evidence is currently not clearly defined (e.g., de Boer et al., 2006; Sarimski, 2003; Varley, 1984). Further domain analysis of the Social Communication Questionnaire, including only those individuals who met cut off scores for ASD on this measure, indicated no significant group differences, suggesting that impairments in social interaction in Sotos syndrome may be associated with the syndrome

more broadly, rather than being specifically associated with the presence of ASD in Sotos syndrome.

Although a small number of studies have previously reported the presence of ASD related behaviors in Sotos syndrome (Leventopolus et al., 2009; Morrow et al., 1990; Zapella, 1990), no standardized assessments have been used and no diagnostic criteria applied explicitly in this population. The present study does indicate a higher prevalence of ASD in participants with Sotos syndrome than might be expected given the level of intellectual disability (evidenced by heightened rates relative to matched contrast groups), but also indicates potential differences in the profile of ASD with evidence of more significant impairment in reciprocal social interaction than repetitive behavior and communication. This warrants further investigation, perhaps using an item level analysis of the SCQ and direct assessments such as the Autism Diagnostic Observation Schedule (Lord et al., 1997). This line of enquiry might indicate further differences in the profile of the triad of impairments and the reasons for endorsement of specific items (see Moss & Howlin, 2009). As for other syndromes it is entirely possible that an ASD profile at a behavioral level is underpinned by differences in score profiles and cognitive or social impairments.

On the Mood and Interest & Pleasure subscales, participants with Sotos syndrome scored significantly higher in comparison to participants with ASD, indicating that levels of affect and interest in the surrounding environment are heightened in individuals with Sotos syndrome relative to those with ASD. Given, the high levels of ASD characteristics reported in the Sotos syndrome group and the comparable difficulties with regard to social interaction, these differences in mood and pleasure are interesting. Studies of mood have not previously been reported within the Sotos syndrome literature and therefore these findings are a novel addition.

The behavioral profiles in Figure 1, illustrate the characteristics of repetitive behavior of the syndrome groups. In keeping with the findings from the SCQ, stereotyped behavior was significantly lower in individuals with Sotos syndrome relative to the ASD group, Interestingly, individuals with Sotos syndrome showed a heightened frequency of preference for routine, repetitive questions and repetitive phrases/signing relative to the Down syndrome group. These behaviors are also seen in combination in Prader-Willi syndrome, in the absence of high levels of other repetitive behaviors, and are related to a specific executive function deficit of attention switching (Moss et al., 2009; Woodcock, Oliver & Humphreys, 2009). Previous studies have reported ritualistic, repetitive and stereotyped behaviors in individuals with Sotos syndrome (e.g. Mourisden & Hansen, 2002; Trad et al., 1991; Rutter & Cole, 1991). However, the specific topographies of these behaviors, identified in the current study, have not previously been reported.

It is important to consider the findings of the current study within the context of a number of methodological limitations. Firstly, the use of survey data is advantageous in that a number of different environments known to the informant across time and larger groups can be sampled. However, it relies upon retrospective reporting, which can be problematic. Furthermore, the use of questionnaire measures does not have the same level of objectivity as in vivo observational methods. While all of the questionnaire measures used in this study have good inter-rater reliability and face validity, not all of the measures employed have been evaluated for concurrent validity. However, these problems are evident across the groups studied and so are unlikely to account for the differences reported. Secondly, as participants were recruited predominately from support groups and clinics, it could be argued that the samples are biased. Indeed, Hyman et al. (2002) hypothesize that individuals caring for a people with challenging behavior are more likely to become members of support groups. However, if apparent, this bias is comparable across all groups and thus any comparisons of behavior

between and across the syndrome groups remains valid. Thirdly, behaviors which seem more frequent in Sotos as compared to Down syndrome need to be seen in the context that the same behaviors are of low frequency in Down syndrome. Thus, placing behaviors reported in the present study, relative to the Prader-Willi syndrome and ASD groups in addition to the Down syndrome group, allows behaviors reported in participants with Sotos syndrome to be compared across groups. Finally, the relatively small sample sizes within the groups make it more difficult to make inferences about the behaviors reported. However, in comparison to the majority of previous studies on Sotos syndrome (e.g. Sarimski, 2003; Finegan et al., 1994), the sample size of participants with Sotos syndrome in the present study is larger.

Combining the findings in this current study, the present study has provided additional support and expanded previous research on the behavioral difficulties seen in Sotos syndrome such as aggression, hyperactivity and Autism Spectrum Disorder. It has also highlighted a number of areas that would benefit from further investigation and consequently further our understanding of the behavioral phenotype of Sotos syndrome.

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FIGURE CAPTION:

Figure 1: Mean item level scores as behavioural profiles on the Repetitive Behaviour Questionnaires for Sotos syndrome (SS), Down syndrome (DS), Prader-Willi syndrome (PWS) and Autism Spectrum Disorder (ASD).

Table I Demographic characteristics, mean age (and standard deviation), statistical analyses and post hoc analyses for participant groups: Sotos Syndrome (SS), Prader-Willi (PWS), Down Syndrome (DS) and Autism Spectrum Disorder (ASD)

		SS	**PWS**	**DS**	**ASD**	**F/X²**	**df**	***p* value**	**Post hoc analyses**
N*		38	38	38	36				
Age**	Mean (SD) Range	17.3 (9.36) 6.34 - 43.49	17.16 (9.49) 5.32-44.33	18.29 (9.79) 6.34 – 43.49	16.34 (8.12) 6.70 – 42.60	0.28	3	0.84	NS
Gender	% Male	65.8	60.5	65.8	77.8	2.67	3	0.45	NS
Self Help[a]	% Partly able/able[b]	84.2	86.1	89.5	83.3	0.68	3	0.88	NS
Mobility[a]	% Mobile[c]	89.5	66.7	94.7	91.4	12.99	***	0.02	DS,SS,ASD>PWS
Vision[a]	% Normal	73.7	69.4	57.9	83.3	6.00	3	.112	NS
Hearing[a]	% Normal	73.7	94.4	65.8	97.2	18.30	3	<.001	ASD, PWS > DS, SS
Speech[a]	% Verbal/partly verbal	97.3	97.1	94.7	94.1	0.95	***	0.86	NS

*N may vary across analysis due to missing data
** In years
*** Fishers exact
[a] Data derived from the Wessex Scale (Kushlick et al. 1973)
[b] Those scoring six or above on the total score of the self help subscale (items g-i).
[c] Those scoring six on the total score of the mobility subscale (items e & f).

Table II Percentage of individuals showing self-injury, physical aggression, stereotyped behaviours and destruction of property in Sotos Syndrome (SS), Prader-Willi (PWS), Down Syndrome (DS) and Autism Spectrum Disorder (ASD)

	Self Injurious Behaviour					**Stereotyped Behaviour**					**Physical Aggression**					**Destruction of Property**				
Group	**%** (*n*)	**Odds ratio (99% CIs)** (*n*)	**X^2**	***p* value**	**Post Hoc Contrast**	**%** (*n*)	**Odds ratio (99% CIs)** (*n*)	**X^2**	***p* value**	**Post Hoc Contrast**	**%** *(n)*	**Odds ratio (99% CIs)** (*n*)	**X^2**	***p* value**	**Post Hoc Contrast**	**%** *(n)*	**Odds ratio (99% CIs)** (*n*)	**X^2**	***p* value**	**Post Hoc Contrast**
SS	42.1 (16)	**8.48 (1.45-49.60)**	**30.39**	**<0.001**	PWS>SS>DS ASD>DS	43.2 (16)	1.87 (0.53-6.57)	**20.71**	**<0.001**	ASD>SS, PWS, DS	43.2 (16)	**6.48 (1.30-32.33)**	7.39	0.06	NS	43.2 (16)	**6.48 (1.30-32.33)**	**18.51**	**<0.01**	SS, ASD, PWS >DS
PWS	68.4 (26)	**25.28 (4.22-151.64)**				50.0 (19)	2.45 (0.70-8.52)				52.6 (20)	**7.65 (1.55-37.83)**				47.4 (18)	**7.65 (1.55-37.83)**			
ASD	52.8 (19)	**13.04 (2.22-76.73)**				80.6 (29)	**10.17 (2.45-42.21)**				58.3 (21)	**10.63 (2.12-53.30)**				55.6 (20)	**10.63 (2.21-53.30)**			
DS	7.9 (3)	-				28.9 (11)	-				28.9 (11)	-				10.5 (4)	-			

* Missing data for one participant

Odds ratios and 99% confidence intervals are shown to demonstrate the likelihood of individuals in each syndrome group showing self-injury, stereotyped behaviour, physical aggression and destruction of property compared with the Down syndrome group. Significant results are indicated in bold type.

Table III Mean (Standard Deviation) scores for subscales of the TAQ, MIPQ, SCQ and SQID with results from ANOVA and Kruskal-Wallis tests and post hoc analyses for Sotos syndrome, Prader-Willi syndrome, Down syndrome & Autism Spectrum Disorder

	SS	**PWS**	**DS**	**ASD**	F/ X^2	*df*	*p* value	**Post -hoc contrasts (<.05)**
TAQ								
Impulsivity	14.56 (7.27) (0.00-24.00)	13.62 (6.80) (0.00-24.00)	7.71 (6.25) (0.00-24.00)	18.22 (5.68) (4.00-24.00)	16.53	(3,149)	<0.001	ASD>PWS>DS SS>DS
Overactivity	11.06(8.51) (0.00-33.00)	7.55 (6.27) (0.00-33.00)	7.14 (7.90) (0.00-36.00)	18.88 (9.69) (4.00-36.00)	16.30	(3,148)	<0.001	ASD >DS, PWS, SS
Impulsive Speech	4.97 (3.97) (0.00-12.00)	5.23 (3.51) (0.00-12.00)	3.41 (3.31) (0.00--12.00	5.09 (4.16) (0.00-12.00)	1.75	(3,133)	0.16	NS
Total TAQ	27.50 (16.00-44.00)	26.25 (15.00- 35.25)	14.00 (7.75 - 23.75)	43.00 (29.75 - 52.75)	28.97	(3,147)	<0.001	ASD>PWS,SS,DS SS>DS
MIPQ-S								
Total MIPQ-S	37.72 (6.53) (14.00 - 48.00)	35.39 (6.63) (21.00- 48.00)	39.74 (6.31) (15.00 - 48.00)	31.38 (6.52) (19.00 - 44.00)	31.94	(3,148)	<0.001	DS>PWS,ASD SS>ASD
Mood	20.70 (3.14) (11.00- 24.00)	19.95 (3.14) (11.00-24.00)	21.11 (3.24) (5.00 - 24.00)	17.88 (3.45) (11.00 - 23.00)	23.31	(3,148)	<0.001	DS,SS>ASD
Interest and Pleasure	17.01 (4.12) (3.00-24.00)	15.45 (4.43) (7.00-24.00)	18.63 (4.03) (8.00-24.00)	7.82 (2.26) (8.00-22.00)	10.19	(3,148)	<0.001	DS>PWS,ASD SS>ASD

SCQ								
Communication	6.18 (2.30) (1.00-11.00)	5.87 (2.30) (1.00 - 11.00)	4.46 (2.80) (0.00-11.00)	7.80 (2.27) (4.00-12.00)	9.30	(3,137)	<0.001	ASD>PWS,DS
Restricted, repetitive & stereotyped behaviour	3.59 (2.64) (0.00-8.00)	3.93 (2.04) (0.00-8.00)	2.33 (2.05) (0.00-7.00)	5.53 (1.89) (1.00-8.00)	13.29	(3,147)	<0.001	ASD>SS,PWS,DS PWS>DS
Reciprocal social interaction	7.61 (3.91) (1.00-14.00)	5.43 (4.06) (0.0-14.00)	4.69 (4.02) (0.00-14.00)	8.38 (3.19) (3.00-15.00)	7.24	(3,138)	<0.001	ASD>PWS,DS SS>DS
Total SCQ	18.50 (12.50-26.18)	16.40 (11.00-23.00)	10.71 (6.75-21.25)	24.00 (18.00-26.90)	18.72	3	<0.001	ASD>SS,PWS,DS SS>DS

Table IV Proportions of participants with Sotos syndrome, Prader-Willi syndrome, Down syndrome and ASD attaining cut-off scores on the Social Communication Questionnaire indicative of ASD or Autism

	SS[1]	PWS[2]	DS[3]	ASD[4]
ASD cut off				
N	26	20	10	36
%	70.3	60.6	31.3	100.0
Autism cut off				
N	12	9	3	20
%	32.4	27.3	9.4	55.6

[1] Data missing for 1 participant
[2]Data missing for 5 participants
[3] Data missing for 7 participants
[4] Data missing for 2 participants

Table V Mean scores, standard deviations, statistical analyses and post hoc analyses on full scale and sub scale level scores of the Repetitive Behaviour Questionnaire for all participant groups Sotos Syndrome (SS), Prader-Willi (PWS), Down Syndrome (DS) and Autism Spectrum Disorder (ASD)

	Syndrome Group				**F**	***df***	***p* value**	**Post-hoc contrasts**
	SS (*n*=38)	PWS (*n*=38)	DS (*n*=38)	ASD (*n*=36)				
	Mean (SD) *Range*							
Stereotyped Behaviour	2.68 (2.74) *0.00-8.00*	3.34 (3.73) *0.00-12.00*	2.81 (3.97) *0.00-12.00*	6.94 (3.76) *0.00-12.00*	11.61	3,149	<.001	ASD>SS,DS,PWS
Compulsive behaviour	5.56 (5.55) *0.00-18.00*	6.27 (5.88) *0.00-19.00*	4.27 (6.40) *0.00-25.14*	8.53 (6.32) *0.00-23.00*	3.20	3,148	.025	ASD>DS
Insistence on sameness	3.03 (2.70) *0.00-8.00*	3.68 (2.36) *0.00-8.00*	2.21(2.95) *0.00-8.00*	4.44 (2.69) *0.00-8.00*	4.65	3,147	.004	ASD> DS
Restricted Preferences*	4.62 (3.89) *0.00-12.00*	4.60 (3.64) *0.00-11.00*	2.94 (3.18) *0.00-12.00*	5.00 (4.04) *0.00-12.00*	2.07	3,134	.11	
Repetitive speech*	5.21 (4.12) *0.0-12.00*	4.86 (3.84) *0.00-12.00*	2.12 (2.84) *0.00-12.00*	5.75 (4.37) *0.00-12.00*	6.02	3,133	.001	SS,PWS,ASD>DS
Verbal total score*	21.54 (16.03)*0.00-56.00*	23.30 (15.16) *2.00-56.00*	14.48 (15.81) *0.00-66.00*	30.63 (16.17) *0.00-66.00*	5.82	3,132	.001	ASD>DS
Total score	21.04 (15.61) *0.00-56.00*	22.20 (15.08) *2.00-56.00*	14.01 (15.10) *0.00-66.00*	29.78 (15.48) *0.00-61.00*	6.57	3,146	<.001	ASD>DS

* Analysis only includes participants who are verbal

Table VI – Analysis of mean scores (standard deviations), statistical analyses and post hoc analyses on item level scores of the Repetitive Behaviour Questionnaire for all participant groups Sotos Syndrome (SS), Prader-Willi (PWS), Down Syndrome (DS) and Autism Spectrum Disorder (ASD)

	Syndrome Groups							
	SS *(n = 34)*	**PWS** *(n=35)*	**DS** *(n= 34)*	**ASD** *(n=32)*	**χ2**	**df**	*p* value	Post-hoc contrasts (*p*<.01)
Stereotyped behaviour								
Q1 Object Stereotypy	0.58 (1.18)	1.21 (1.70)	1.18 (1.72)	2.42 (1.61)	24.10	3	<.001	ASD>SS, DS, PWS
Q2 Body Stereotypy	0.50 (1.13)	0.79 (1.51)	0.84 (1.48)	2.19 (1.74)	25.70	3	<.001	ASD>SS, DS, PWS
Q3 Hand Stereotypy	1.61 (1.76)	1.34 (1.74)	0.79 (1.56)	2.33 (1.72)	17.72	3	.001	ASD> DS
Compulsive behaviour								
Q4 Cleaning	0.37 (1.10)	0.71 (1.43)	0.37 (1.50)	0.75 (1.44)	4.36	3	.225	NS
Q5 Tidying	0.71 (1.23)	0.29 (0.84)	0.50 (1.06)	0.89 (1.19)	8.87	3	.031	NS
Q6 Hoarding	0.96 (1.37)	1.58 (1.52)	0.42 (0.95)	0.69 (1.21)	17.12	3	.001	PWS>ASD,DS
Q7 Organising Objects	0.55 (1.06)	2.63 (1.54)	0.40 (0.84)	0.83 (1.28)	2.61	3	.457	NS
Q12 Rituals	0.41 (1.06)	0.50 (1.08)	0.58 (1.31)	1.50 (1.78)	11.99	3	.007	NS
Q16 Lining up objects	1.27 (1.52)	0.87 (1.28)	0.82 (1.37)	1.11 (1.45)	2.76	3	.432	NS
Q18 Completing behaviour	0.92 (1.44)	1.24 (1.55)	0.76 (1.32)	1.58 (1.73)	5.64	3	.131	NS
Q19 Spotless behaviour	0.38 (0.98)	0.54 (1.18)	0.42 (1.11)	1.17 (1.66)	7.34	3	.062	NS

Restricted preferences								
Q8 Attachment to people*	1.79 (1.63)	1.46(1.54)	1.44 (1.46)	1.36 (1.64)	1.51	3	.679	NS
Q10 Attachment to objects	1.18(1.61)	1.29 (1.59)	0.82 (1.43)	1.25 (1.73)	2.56	3	.465	NS
Q13 Restricted conversation*	1.82 (1.74)	1.83 (1.69)	0.68 (1.34)	1.94 (1.88)	11.46	3	.009	NS
Insistence on sameness								
Q15 Preference for routine	2.14 (1.62)	2.58 (1.62)	1.11 (1.57)	2.86 (1.42)	22.89	3	<.001	SS,ASD, PWS>DS;
Q17 Just right behaviour	0.92 (1.46)	1.11 (1.33)	1.12 (1.57)	1.58 (1.65)	4.61	3	.203	NS
Repetitive speech								
Q9 Repetitive questions*	2.56 (1.58)	2.63 (1.54)	1.32 (1.65)	1.69 (1.89)	13.67	3	.003	SS, PWS>DS
Q11 Repetitive phrases/signing	1.35 (1.80)	1.29 (1.66)	0.26 (0.95)	1.97 (1.78)	21.53	3	<.001	SS, ASD,PWS>DS
Q14 Echolalia*	1.34 (1.60)	0.94 (1.45)	0.62 (1.35)	1.67 (1.66)	10.40	3	.015	NS

*Analysis only includes participants who are verbal
Mean Scores reported; median scores are uninformative with too many zeros

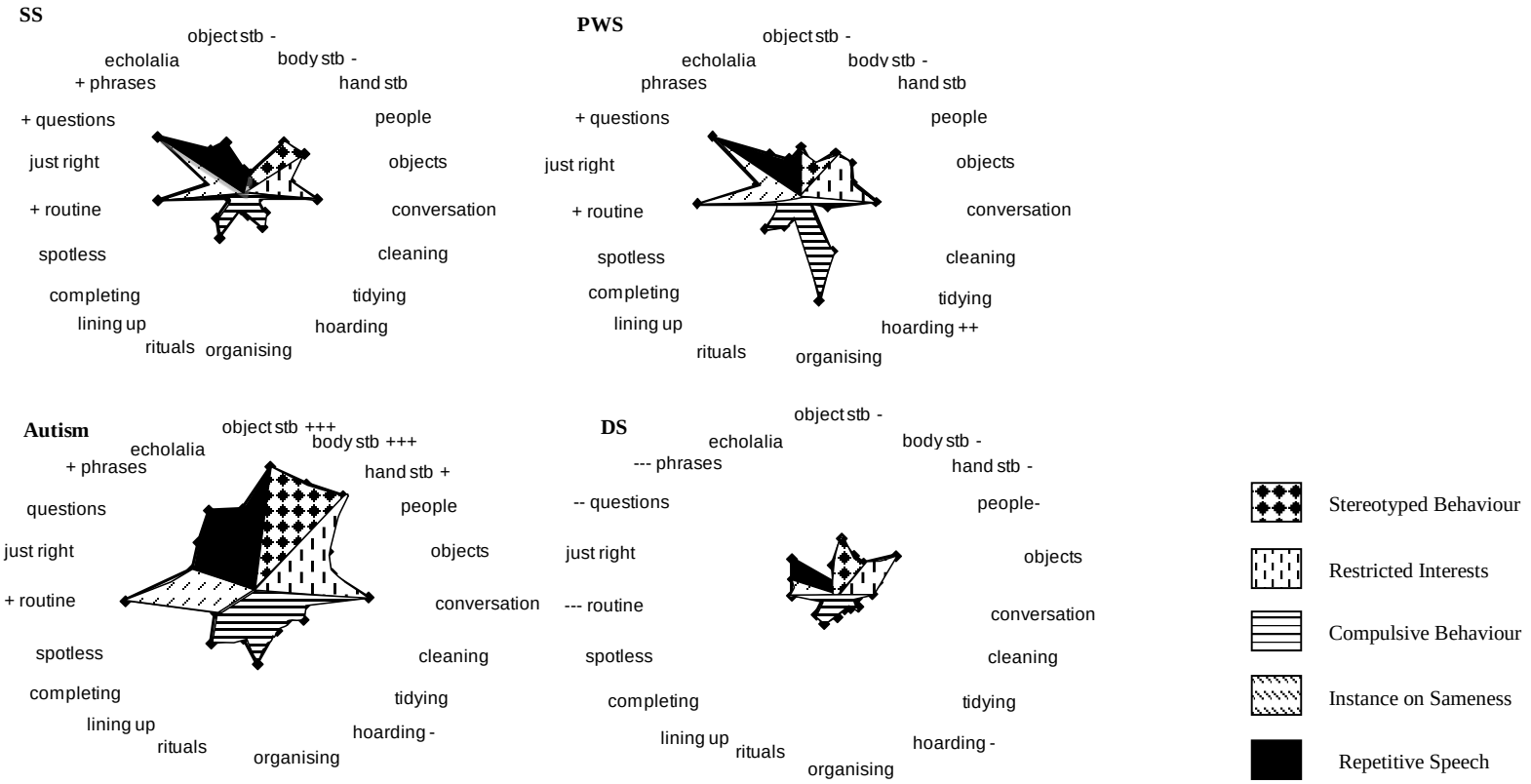

Figure 1: Mean item level scores as behavioural profiles on the Repetitive Behaviour Questionnaires for Sotos syndrome (SS), Down syndrome (DS), Prader-Willi syndrome (PWS) and Autism Spectrum Disorder (ASD).
Scores of "+" indicate high specificity (+2 or more groups) while "- " highlights low specificity (-2 or more groups)